TOPAS-nBio: A Monte Carlo simulation toolkit for cell-scale radiation effects

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Abstract:
TOPAS-nBio is an extension of the TOPAS (TOol for PArticle Simulation) Monte Carlo system to the (sub-)cellular level. TOPAS provides a user-friendly interface to the general purpose Geant4 toolkit specifically designed for medical physicists and applications in radiation therapy. TOPAS-nBio employs the same user-friendly approach to provide an interface to, and extend the capabilities of, the Geant4-DNA project, including the low energy domain of radiation effects and initial radiation chemistry on biological structures such as DNA. The goal is to shed light on the fundamental mechanisms that determine the biological outcome of irradiated tissue and understand the differential response of tissue to various types of radiation such as photons, light ions (proton or Carbon) and heavier ions (iron and silicon). This is relevant to radiotherapy applications as well as understanding space radiation effects on astronauts.
TOPAS-nBio offers a multitude of geometric implementations of biological structures (e.g. cells, mitochondria and DNA) to allow users to develop realistic representations of the tissue in question. Additionally, a significant effort was made to improve the simulation of the initial chemical reactions of radiolysis products. Finally, mechanistic models of the DNA repair kinetics can be linked to TOPAS-nBio to determine the likelihood of repair or misrepair of the radiation-induced DNA damage patterns via the Standard for DNA Damage (SDD) data format.
TOPAS-nBio is released as an open source extension to the TOPAS toolkit. By providing a select catalogue of cell geometries and repair models, we hope to encourage an active contribution by the research community to continuously expand the capabilities of TOPAS-nBio and eventually help improve our understanding of radiation response from the bottom up.

1. Introduction:

Radiation is a double-edged sword. On the one hand, we use radiation to kill tumor cells in radiation therapy employing, for example, external beam radiation therapy using photons, protons and light ions (mostly Carbon). On the other hand, radiation may induce mutations in the DNA of cells, resulting in either acute or late toxicities as a side effect of radiation therapy or from environmental exposures (e.g. on earth or in space).

As manned exploratory missions increase in both duration and distance from the Earth's protective magnetosphere, astronauts will be exposed to a spectrum of ionizing radiation, comprised of galactic cosmic rays (GCR) and solar cosmic radiation (SCR). High atomic number and energy (HZE) particle exposure, even in low fluences, is a particular concern for human health in space. HZE particles deposit dense tracks of ionization events that are believed to cause significant biological damage in cells and tissue that is difficult to repair. Exposure to HZE particles are inevitable outside Earth's orbit since they are likely to penetrate current shielding on spacecrafts. Health risk concerns from GCR as well as SCR are thought to include bone loss (Macias et al., 2016) (further exacerbated by microgravity), cognition dysfunction (Parihar et al., 2015), cardiovascular system damage (White and Averner, 2001), radiation-induced cataracts (Blakely and Chang, 2007) and cancer risks.

The effects of radiation on tissue are typically modeled as a function of dose and potentially adding dose-modifying properties, e.g. the ionization density of the radiation modality, i.e. the linear energy transfer (LET). This concept has worked well in radiation therapy, where most tumors can be assumed to be radioresistant, and in radiation protection, where a cautious approach offers stringent safety regulations. However, calculations that only consider physical properties of the radiation modality (e.g. dose and LET) can only serve as an approximation of the expected biological outcome (Paganetti et al., 2019). Such broad approximations offer conservative estimations of the variations that we know exist to ensure that we do not overestimate the cell killing in radiation therapy or underestimate the effect for radiation protection. However, many studies have shown, for example, that the RBE of proton therapy is not constant but instead varies across the treatment field, increasing with decreasing proton energy or increasing LET. Independent of biological parameters, radiation seems to be more effective at cell killing with increasing LET (Paganetti, 2014).

Despite the large variations caused by physical parameters of the incident radiation, biological parameters seem to be even more important when determining the relative observed outcome (Held et al., 2016). The radio-sensitivity of the irradiated tissue depends on multiple factors, including the tissue type (e.g. the cell line, fast or slow responding), repair deficiencies due to mutations (e.g. homologous end-joining (HR) deficient cells), and the general microenvironment (e.g. in vitro vs. in vivo, oxygenation levels).

In order to fully optimize radiation therapy or radiation protection calculations, one needs to understand the connections between the physical radiation properties, the resulting chemical reactions, and their impact on the cell-type dependent biological repair processes. One way to capture the fundamental mechanisms that determine biological outcome is to combine track-structure based Monte Carlo simulations (capturing physics processes down to eV levels), simulation of initial chemical reactions (to include indirect, i.e. chemically-induced, cell damage), and a mechanistic approach of cell repair processes.

Here we present an overview of the TOPAS-nBio Monte Carlo toolkit (Schuemann et al., 2019a). TOPAS-nBio aims to offer track-structure based Monte Carlo simulations to determine biological effects by including initial chemical reactions and linking to mechanistic repair models via the recently developed Standard for DNA Damage (SDD) data format (https://standard-for-dna-damage.readthedocs.org, (Schuemann et al., 2019b)). TOPAS-nBio has recently been released (see https://topas-nbio.readthedocs.org) and is an open-source extension to TOPAS (Tool for Particle Simulation, https://topas.readthedocs.org, (Perl et al., 2012)). Thus, TOPAS-nBio offers a flexible, mechanistic modeling framework of cell-scale response to radiation damage with an intuitive control system.

2. Methods:

2.1 The basis of TOPAS-nBio

TOPAS (Perl et al., 2012) is an application aimed to facilitate Monte Carlo simulations layered on top of the Geant4 Monte Carlo system (Agostinelliothers, 2003; Allison et al., 2006; 2016). TOPAS-nBio (Schuemann et al., 2019a) is the nanodosimetric equivalent, providing an interface to the Geant4-DNA package (Incerti et al., 2010a; 2010b; Bernal et al., 2015; Incerti et al., 2018), and offering additional features via a graphical user interface or control via text-based parameter files. The overall goal of the TOPAS and TOPAS-nBio control system is to make Monte Carlo simulations accessible to researchers in the fields of radiation physics and biology by removing the requirement of having to be experts in programming or the Monte Carlo method. TOPAS-nBio offers a large range of pre-defined cell geometries, scoring options and chemical reactions that users can combine to create their simulation experiment. In addition, since not all use cases can be anticipated, a method to integrate user-written code segments was developed. Advanced users are encouraged to extend the functionality by designing new geometries or scorers following available templates. The flexibility of this extension system is demonstrated by TOPAS-nBio, which is built nearly entirely as a collection of extension classes that required only a few additions to the TOPAS core. The TOPAS-nBio extension package is supported starting with TOPAS version 3.2 which is layered on top of Geant4 version 10.5.p1. A detailed list of parameter options and settings available in TOPAS and TOPAS-nBio can be found on the respective Read the Docs websites listed above.

2.2 Physics & Chemistry

TOPAS-nBio is designed for nanometer scale simulations based on Geant4 physics settings provided by the Geant4-DNA collaboration. In the current release of Geant4 (v.10.5.p1), this includes the default G4EmDNAPhysics constructor as well as 8 additional options (G4EmDNAPhysics_option1-8). TOPAS-nBio lets users select between these modular physics options, each of these includes a given set of constructors combining different physics models for low energy processes. In addition, users can select physics settings where the kinetic energy of the incident particle is artificially kept constant (frozen-velocity approximation) after each scattering processes (Incerti et al., 2018).
The TsEmDNAPhysics constructor was created to provide additional flexibility and proton cross sections for energies up to 500 MeV. This module allows users to selectively combine the physics models available in Geant4-DNA, controlling which model is involved in each physics

process. For example, one can combine the elastic models of the CPA100 model (option 4) with the inelastic models from Emfietzoglou (option 6). The energy cuts for electron capture or solvation are automatically readjusted depending on the energy limits of the physics models. The default settings of the TsEmDNAPhysics lists were optimized to provide the best agreement to experimental G-values (Ramos-Méndez et al., 2018) when simulating chemistry processes. The simulation of radiolysis, including the initial physico-chemical and chemical reactions induced by radiation, are offered by the Geant4-DNA toolkit via the chemistry constructor. In addition, TOPAS-nBio offers an updated set of reaction rates based on (Ramos-Méndez et al., 2018) via the TsEmDNAChemistry module as well as an extended list of reactions including, for example O_2 reactions, in the TsEmDNAChemistryExtended module.

2.3 Geometries and scoring

To investigate effects of radiation and the following chemical reaction on cells, various cell geometries have been developed within the TOPAS-nBio toolkit or adapted from previous Geant4-DNA developments (McNamara et al., 2017; 2018). Different levels of accuracy for simulating biological effects can be achieved by combining these geometries in a modular way. Users can select a cell shape, add mitochondria or lysosomes, define a nucleus and add DNA content using different geometrical representations of the DNA (see Figure 1). Special geometries are offered for select cell lines, including osteoclasts and osteoblasts. An interface to the Neuromorpho.org database, which contains over 100,000 geometric representations of neurons from various species, including humans, offers the further possibility to simulate effects of radiation on neurons.

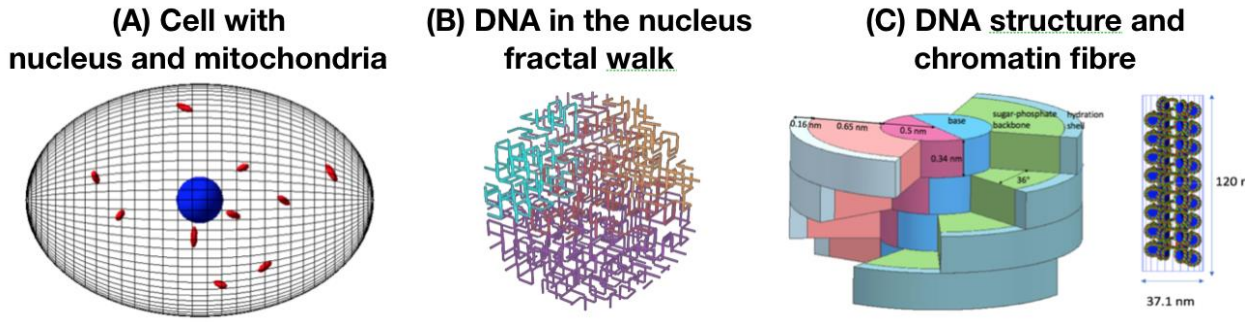

Figure 1: Cell representation with nucleus and mitochondria (A), DNA filling the nucleus with a fractal walk pattern (B), and the chromatin structure with hydration shell (C).

All geometries and the corresponding parameters are described on the TOPAS-nBio Read the Docs website and can be controlled via the TOPAS Parameter Control System. If users require additional geometries, users are again referred to the option of writing extensions which can be contributed back to be included in TOPAS-nBio.

In order to determine the biological outcome, multiple scorers and filters (for selective scoring) are provided by the main TOPAS system. However, the most commonly used scoring option for DNA scale simulations is using the ntuple (tabulated) format, which allows post-processing of the results to investigate the structure of, for example, DNA damage with various assumptions. One special scoring option is the standard for DNA damage (SDD). This cross-platform standard (Schuemann et al., 2019b) has been designed to link simulations of DNA damage induction to

DNA repair models. The SDD further allows for a well-defined cross-platform comparison of track structure Monte Carlo simulations as well as DNA repair models. Additional options to score DNA damages as double strand breaks (DSBs) are provided for select DNA geometries. Due to differences in the underlying geometry implementations between the DNA models, currently each of these scorers is linked to a specific geometry.

Results

Several studies showing the performance of TOPAS-nBio have already been published (McNamara et al., 2017; Underwood et al., 2017; McNamara et al., 2018; Ramos-Méndez et al., 2018; Schuemann et al., 2019a). Here, we briefly summarize a few of these results to highlight the features of TOPAS-nBio.

3.1 G-values

One important step to advance the modeling approach from simulations of pure particle track-structures towards predicting biological outcome of a cell is the inclusion of chemical processes. In a well oxygenated cell, about 50-90% of the DNA damage is not caused by direct interactions of the radiation field with the DNA but by damages induced by secondary radiolysis products that react with DNA components (la Fuente Rosales et al., 2018).

In order to assess the performance of the implemented chemical reaction rates, the best experimental data available is measurements of G-values, i.e. the number of molecules produced by the deposition of 100 eV of the initial radiation. We compared the G-values of several molecules over time with measurements from various experiments. In order to better describe the experimental data, both the physics list and the chemical reaction rates have been updated from the original Geant4-DNA values in a TOPAS-nBio specific physics (TsEmDNAPhysics) and chemistry (TsEmDNAChemsitry) list. Additionally, TOPAS-nBio allows users to adjust the reaction rates and define new reactions via the parameter system in order to further allow users to match their own preferred experimental data.

Chemical reactions in Geant4-DNA are handled in a step-by-step approach that requires long computation times. TOPAS-nBio additionally implemented an option to simulate chemistry via the independent reaction time (IRT) method (Clifford et al., 1986; Green et al., 1990). IRT greatly reduces the calculation time of the chemical processes and provides G-values of similar accuracy to the step-by-step approach (see Figure 2).

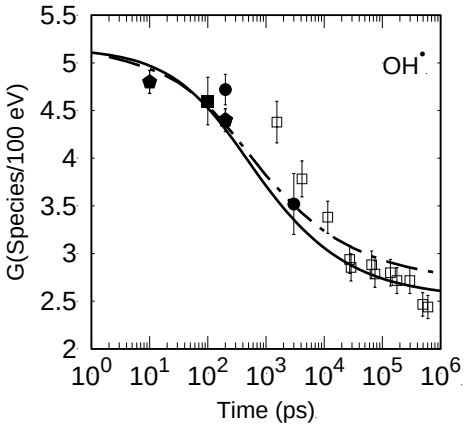

Figure 2: G values as a function of time for TOPAS-nBio step-by-step simulation (dash-dot line) and IRT (solid line), calculated for 1 MeV electrons. Experimental data from (LaVerne, 2000), (Jay-Gerin and Ferradini, 2000), and (Jonah and Miller, 1977).

3.2 DNA damage induction and uncertainties of parameter variations

TOPAS-nBio offers a large variety of geometries, scorers, physics and chemistry settings. We have applied TOPAS-nBio to predict DNA damage induction frequencies for DNA plasmids and compared our results to experimental data (McNamara et al., 2017). However, even for these

relatively simple geometries without repair mechanisms, we found that uncertainties arising from, for example, geometry assumptions and differences between simulation and experimental setup greatly influence the predictions. Simulating the more complex and dynamic environment of a live cell induces additional uncertainties. The predicted biological effect of radiation damage also depends on the implemented physics models, the simulated time of the chemical phase, the chemical reactions considered, the thresholds to induce DNA damages, and many more. Figure 3 shows the effect of a few parameter choices on the induction of DSB.
The default TOPAS-nBio physics model (TsEmDNAPhysics) is identical to the default Geant4-DNA physics model, but users could choose different processes for different particles in their parameter files such as:

sv:Ph/Default/Modules = 1 "TsEmDNAPhysics"
s:Ph/Default/Electron/SetElasticScatteringModel = "CPA100"

In the DNA damage simulation, most of the direct damages are caused by secondary electrons, and the impact of electron elastic scattering model on the DNA damage yield was simulated. The electron elastic scattering model was set as default ("Champion") or "CPA100" model. As shown in Figure 3A, using the "CPA100" model will predict higher DSB and SSB yield than the "Champion" model.

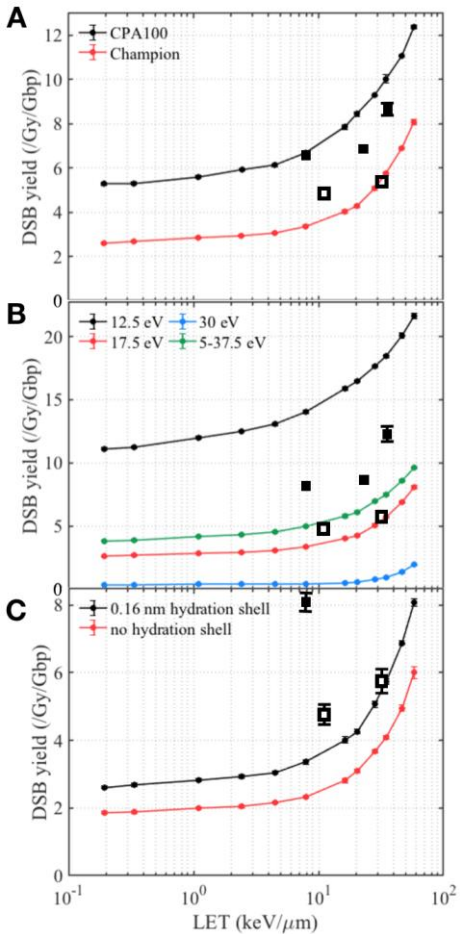

Figure 3:DNA damage results simulated with different electron elastic models (A), different direct damage thresholds (B), and with/without a 0.16 nm thick hydration shell (C). Data from (Frankenberg et al., 1999) □, and (Belli et al., 2000) □.

Similarly, various energy deposition thresholds to induce DNA damages were used in different studies (Nikjoo et al., 2001; Friedland et al., 2011; 2017; Meylan et al., 2017; Lampe et al., 2018; Mokari et al., 2018). The impact of using different thresholds is presented in Figure 3 B. Considering ionizations in the hydration shell could further cause direct damage in the backbone (Meylan et al., 2017). The impact of including a hydration shell (with a thickness of 0.16 nm) was simulated and the results are presented in Figure 3 C.
Understanding these uncertainties and the importance of different parameter choices is important when reporting predictions of biological outcome. The introduction of the SDD (Schuemann et al., 2019b) facilitates cross platform comparison of radiation induced DNA damage patterns and the resulting predicted biological effects. We anticipate that the SDD will be essential to tease out model-dependent vs. model-independent parameter uncertainties and, thereby, determine which processes are most significant for DNA repair.

3.3 Extensions & Interfaces by others

The TOPAS-nBio release (based on TOPAS version 3.2, Geant4 version 10.5.p1) provides DNA damage patterns and offers scoring of other quantities at the (sub-)cellular level. In parallel to

our efforts to develop fully track-structure based radiation induced damages to various cell components, other groups have been developing mechanistic models of DNA repair kinetics. Two of these models, the McMahon model (McMahon et al., 2016; 2017) and DaMaRiS developed in Manchester (Henthorn et al., 2018; Warmenhoven et al., 2018; Ingram et al., 2019), have been linked to TOPAS-nBio. While the McMahon model integrates TOPAS-nBio results via the SDD, DaMaRiS has been implemented as part of the TOPAS-nBio package and is available to users via the extension manager in TOPAS. With these extensions, TOPAS-nBio offers mechanistic simulations from track structure to observable biological endpoints.

Discussion

TOPAS-nBio is designed to study how microscopic cell or sub-cellular damage patterns relate to the observed biological outcome. These effects become most visible when energy depositions are highly localized. Due to the statistical nature of energy depositions, low LET radiation modalities such as photons and high-energy (>100 MeV) protons can often be approximated by a random distribution of energy depositions of damages. While TOPAS-nBio can be used to investigate the effects of low-LET radiation, the optimal simulation scenario includes only a few tracks per cell that causes highly heterogeneous damage patterns, i.e. high-LET radiation. Thus TOPAS-nBio is ideal for simulations at the end-of-range for proton and light-ion therapy (Helium, Carbon), and to investigate low-dose environmental exposures, such as the effects of space radiation on astronauts, which involves a low fluence, typically no more than a single track per cell per day (i.e. within a full repair cycle) and high-LET radiation, e.g. the high-LET components of the primary GCR and secondary fragments produced by primary interactions in shielding.

In an ideal scenario, one could determine the biological outcome of a cell given sufficient information of the radiation damage and the cells. However, there are large gaps in length and time scales between the physical, chemical and biological simulations. Additionally, it is extremely difficult to separate biological processes into each mechanistic step at short time scales. Typical available endpoints are, for example, foci formation data that count the activity of certain proteins within an imaging spot of several 100 nm obtained several minutes to hours post-irradiation, or colony formation experiments that simply count the viability of cells days after the irradiation procedure. Significant assumptions have to be made about the processes leading from one point to another, which are incorporated in systematic uncertainties in repair model parameters.

TOPAS-nBio provides one step along the way to a more detailed understanding of the mechanisms underlying cellular response to radiation damage. Applying track structure simulations combined with modeling of chemical and biological processes allows to investigate trends and test if hypotheses of the underlying mechanisms can describe the observed trends. This approach can be employed to continuously refine the models and thereby advance our understanding of radiation effects from physics towards biology.

Conclusion

The presented simulation toolkit, TOPAS-nBio, wraps and extends the functionality of Geant4-DNA, while removing the need to write and compile new code. At the same time, the flexible extension interface offered within TOPAS allows advanced users to design new features by

adding small code snippets. TOPAS-nBio natively offers a large set of pre-defined geometries, scoring options and modular lists of physics and chemistry reactions. Biological outcome can be obtained by linking DNA repair models via the SDD (Standard for DNA Damage) data format or using models already provided within TOPAS-nBio.

TOPAS-nBio is ideal to investigate effects of radiation modalities with dense track structure (i.e. high LET) and for scenarios of low fluence, e.g. out-of-field effects in radiation therapy and environmental exposure on earth or in space. In addition, studies that compare relative effects (e.g. the ratio of induced DSBs for photon vs. proton irradiation or induced by exposure to a solar particle event vs. galactic cosmic rays) offer more robust predictions. For relative studies, the relatively large, systematic uncertainties, e.g. from physics cross sections at very low energies or for the probabilities in each step of the repair mechanisms, cancel out and allow to estimate trends without accurate knowledge of the absolute effect size.

We hope that TOPAS-nBio will help researchers interested in understanding the connection between physics and biology. The code is released as an open source extension to the TOPAS toolkit, which in turn is offered free of charge to all non-profit users worldwide. Contributions from users developing new geometries, scorers or other features are encouraged and will be included on the TOPAS-nBio website (www.topas-nBio.readthedocs.org). The overall goal is to combine research activities in multiple fields to advance our understanding of the mechanisms of cellular response to radiation exposure.

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